COMPOSITIONS AND METHODS FOR TREATMENT OF ABNORMAL CELL GROWTH

Claim of Priority

This application claims priority to U.S. provisional application 61/925,467, filed on January 9, 2014 and herein referenced in its entirety.

Field of Invention

This invention relates to compositions, for example oral dosage forms, and methods that are useful in the treatment of abnormal cell growth, such as cancer, in mammals, especially humans.

Background of Invention

Convincing evidence suggests that focal adhesion kinase (FAK), a cytoplasmic, non-receptor tyrosine kinase, plays an essential role in cell-matrix signal transduction pathways (Clark and Brugge 1995, *Science* 268: 233-239) and its aberrant activation is associated with an increase in the metastatic potential of tumors (Owens et al. 1995, *Cancer Research* 55: 2752-2755). FAK was originally identified as a 125 kDa protein highly tyrosine-phosphorylated in cells transformed by v-Src. FAK was subsequently found to be a tyrosine kinase that localizes to focal adhesions, which are contact points between cultured cells and their underlying substratum and sites of intense tyrosine phosphorylation. FAK is phosphorylated and, thus, activated in response to extracellular matrix (ECM)-binding to integrins. Recently, studies have demonstrated that an increase in FAK mRNA levels accompanied invasive transformation of tumors and attenuation of the expression of FAK (through the use of antisense oligonucleotides) induces apoptosis in tumor cells (Xu et al. 1996, *Cell Growth and Diff.* 7: 413-418). In addition to being expressed in most tissue types, FAK is found at elevated levels in most human cancers, for example in highly invasive metastases.

Accordingly, a need exists for compounds (*e.g.*, inhibitors), compositions (e.g, formulations, *e.g.*, oral formulations (*e.g.*, oral dosage forms)), and methods of use of inhibitors of the non-receptor tyrosine kinase, FAK, for use in the treatment of abnormal cell growth. U.S. Pat. No. 8,247,411 relates to a broad class of novel pyrimidine derivatives that are kinase inhibitors, and more specifically, inhibitors of FAK. Compounds such as these may be useful in the treatment of abnormal cell growth.

Summary of the Invention

In one ~~aspect~~embodiment, the present ~~invention~~ disclosure comprises a composition, *e.g.*, pharmaceutical composition comprising VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-

6063 hydrochloride), *e.g.,* admixed with an excipient (*e.g.,* a binder, *e.g.,* a polymer, *e.g.,* a precipitation inhibitor, *e.g.,* Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.,* Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.,* HPMCAS-H, HPMCAS-M, HPMCAS-HF); a *e.g.,* polyol (*e.g.,* mannitol-starch (*e.g.,* Pearlitol Flash), mannitol, sorbitol)). In one aspect, there is provided a pharmaceutical composition comprising VS-6063 (*e.g.,* VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.,* VS-6063 hydrochloride), admixed with an excipient (*e.g.,* a binder, *e.g.,* a polymer, *e.g.,* a precipitation inhibitor, *e.g.,* HPMC, *e.g.,* HPMCAS, *e.g.,* HPMCAS-HF; a binder (*e.g.,* polyvinylpyrrolidone (*e.g.,* polyvinylpyrrolidone vinyl acetate copolymer (PVP/VA), Copovidone), other copolymers (*e.g.,* comprising polyethylene glycol, polyvinylcaprolactam, and polyvinylactate (*e.g.,* Soluplus))). In some embodiments, the excipient is a binder. In some embodiments, the excipient is a polymer. In some embodiments, the polymer is a precipitation inhibitor. In some embodiments, the precipitation inhibitor is a HPMCAS. In some embodiments, the precipitation inhibitor is HPMCAS-HF. In some embodiments, the excipient reduces precipitation (*e.g.,* of VS-6063 in solution, *e.g.,* in vivo) when administered orally. In some embodiments, the excipient enhances bioavailability (*e.g.,* improves absorption) of VS-6063 (*e.g.,* VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.,* VS-6063 hydrochloride), when administered orally. In some embodiments, the ratio (*e.g.,* relative amount) by weight of VS-6063 (*e.g.,* VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.,* VS-6063 hydrochloride), to the polymer is about 1 to 1, 1 to 2, 1 to 3, 1 to 4, 1 to 5, 1 to 6, 1 to 7, 1 to 8, or 1 to 9. In some embodiments, the polymer is a precipitation inhibitor, *e.g.,* Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.,* Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.,* HPMCAS-H, HPMCAS-M, HPMCAS-HF). In some embodiments, the VS-6063 (*e.g.,* VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.,* VS-6063 hydrochloride), is present in the composition in an amount that is about 10, 25, 30, 31, 32, 32.5, 33, 34, 35, 40, 45, 50% or more weight per weight (w/w) relative to an amount of polymer, *e.g.,* a precipitation inhibitor, provided. In some embodiments, the composition is admixed with 5 to 50%, 5 to 30%, 10 to 30%, 10 to 20%, 12 to 15%, or 13% weight of VS-6063, or a pharmaceutically acceptable salt thereof, per weight of the composition. In some embodiments, the polymer is present at 25 to 55%, 35 to 45%, 38 to 43%, or 40% weight of polymer per weight of the oral dosage form. In some embodiments, the polymer is a precipitation inhibitor, *e.g.,* Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.,* Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.,* HPMCAS-H, HPMCAS-M, HPMCAS-HF). In some embodiments, the precipitation inhibitor is a HPMCAS. In some embodiments, the precipitation inhibitor is HPMCAS-HF.

In some embodiments, the composition is configured in an oral dosage form. In some embodiments, the oral dosage form comprises 5 to 50%, 5 to 30%, 10 to 30%, 10 to 20%, 12 to 15%, or 13% weight of VS-6063, or a pharmaceutically acceptable salt thereof, per weight of the oral dosage form. In some embodiments, the VS-6063 (*e.g.,* VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.,* VS-6063 hydrochloride), is present at 13% weight of VS-6063, or a pharmaceutically acceptable salt thereof, per weight of the oral dosage form.

times, at least 5 times) greater than a reference dosage form of the same dosage amount (*e.g.*, a dosage form having 100 mg of VS-6063 relative to a reference dosage form also having 100 mg of VS-6063). In an embodiment, the C_{max} value of an oral dosage form described herein is at least 1.6 times greater, at least 1.7 times greater, at least 1.8 times greater, at least 1.9 times greater, at least 2 times greater, at least 3 times greater, or at least 4 times greater than a reference dosage form of the same dosage amount.

In an embodiment, an oral dosage form described herein has a reduced food effect relative to a reference oral dosage form, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture. In an embodiment, the difference between the T_{max} value of the fed and fasted states for subjects administered an oral dosage form described herein is less that the difference between the T_{max} value of the fed and fasted states for subjects administered a reference oral dosage form of the same dosage amount, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture.

In an embodiment, an oral dosage form described herein has consistent exposure when administered to a subject. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 50% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 40%, 30%, 20%, or 10% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount.

In one ~~aspect~~embodiment, the present ~~invention~~ disclosure comprises an oral dosage form comprising: VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride) in an amount from about 5 to 50% by weight on a dry weight basis, a pharmaceutically acceptable excipient (*e.g.*, a binder, *e.g.*, a polymer, *e.g.*, a precipitation inhibitor, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF), in an amount from about 25 to 55% by weight on a dry weight basis, a pharmaceutically acceptable filler (*e.g.*, microcrystalline cellulose, *e.g.*, microcrystalline cellulose PH 102, *e.g.*, Avicel PH102) in an amount from about 10 to 30% by weight on a dry weight basis, a second pharmaceutically acceptable filler (*e.g.*, lactose, *e.g.*, lactose monohydrate, *e.g.*, FastFlo 316) in an amount from about 10 to 30% by weight on a

dry weight basis, a pharmaceutically acceptable disintegrant (*e.g.*, starch, *e.g.*, modified starch, *e.g*, sodium starch glycolate) in an amount from about 0 to 5% by weight on a dry weight basis, and a pharmaceutically acceptable lubricant (*e.g.*, magnesium stearate) in an amount from about 0.1 to 2% by weight on a dry weight basis. In one aspect, there is provided an oral dosage form comprising: VS-6063 (*e.g.*, VS-6063, or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride) in an amount from about 5 to 50% by weight on a dry weight basis, a pharmaceutically acceptable filler (*e.g.*, microcrystalline cellulose, *e.g.*, microcrystalline cellulose PH 102, *e.g.*, Avicel PH102) in an amount from about 10 to 30% by weight on a dry weight basis, a second pharmaceutically acceptable filler (*e.g.*, lactose, *e.g.*, lactose monohydrate, *e.g.*, FastFlo 316) in an amount from about 10 to 30% by weight on a dry weight basis, an additional pharmaceutically acceptable excipient (*e.g.*, a precipitation inhibitor, *e.g.*, HPMC-AS, *e.g.*, HPMC-AS HF) in an amount from about 25 to 55% by weight on a dry weight basis, a pharmaceutically acceptable disintegrant (*e.g.*, starch, *e.g.*, modified starch, *e.g.*, sodium starch glycolate) in an amount from about 0 to 5% by weight on a dry weight basis, and a pharmaceutically acceptable lubricant (*e.g.*, magnesium stearate) in an amount from about 0.1 to 2% by weight on a dry weight basis. In some embodiments, the ~~invention~~ present disclosure comprises an oral dosage form comprising: VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride) in an amount from about 10 to 15% by weight on a dry weight basis, a pharmaceutically acceptable excipient (*e.g.*, a binder, *e.g.*, polymer, *e.g.*, a precipitation inhibitor, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF), in an amount from about 35 to 55% by weight on a dry weight basis, a pharmaceutically acceptable filler (*e.g.*, microcrystalline cellulose, *e.g.*, microcrystalline cellulose PH 102, *e.g.*, Avicel PH102) in an amount from about 15 to 25% by weight on a dry weight basis, a second pharmaceutically acceptable filler (*e.g.*, lactose, *e.g.*, lactose monohydrate, *e.g.*, FastFlo 316) in an amount from about 15 to 25% by weight on a dry weight basis, a pharmaceutically acceptable disintegrant (*e.g.*, starch, *e.g.*, modified starch, *e.g.*, sodium starch glycolate) in an amount from about 2.5 to 3.5% by weight on a dry weight basis, and a pharmaceutically acceptable lubricant (*e.g.*, magnesium stearate) in an amount from about 0.2 to 1.5% by weight on a dry weight basis. In some embodiments, the oral dosage form is a compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet.

In some embodiments, the excipient is one or more binders (*e.g.*, polyvinylpyrrolidone (*e.g.*, polyvinylpyrrolidone vinyl acetate copolymer (PVP/VA), Copovidone), other copolymers (*e.g.*, comprising polyethylene glycol, polyvinylcaprolactam, and polyvinylactate (*e.g.*, Soluplus))). In some embodiments, the binder is a polymer, *e.g.*, a precipitation inhibitor. In some embodiments, the binder comprises two binders (*e.g.*, polyvinylpyrrolidone (*e.g.*, polyvinylpyrrolidone vinyl acetate copolymer (PVP/VA), Copovidone), other copolymers (*e.g.*, comprising polyethylene glycol, polyvinylcaprolactam, and polyvinylactate (*e.g.*, Soluplus))). In some embodiments, the binder is a polymer, *e.g.*, a precipitation inhibitor. In some

embodiments, the binder is present at about 37.5% weight of binder per weight of the oral dosage form. In some embodiments, the binder is present at about 25% weight of binder per weight of the oral dosage form. In some embodiments, the filler is a polyol (*e.g.,* mannitol-starch (*e.g.,* Pearlitol Flash), mannitol, sorbitol).

In some embodiments, the disintegrant is a polyvinylpolypyrrolidone (*e.g.,* crospovidone). In some embodiments, the disintegrant is present at 0 to 30%, 5 to 25%, 5 to 20%, 5 to 15%, or 10% weight of disintegrant per weight of the oral dosage form.

In an embodiment, an oral dosage form described herein has a greater C_{max} value than a reference oral dosage form, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF), in an admixture. In an embodiment, the C_{max} value of an oral dosage form described herein is at least 1.1 times (*e.g.*, at least 1.25 times, at least 1.5 times, at least 2 times, at least 3 times, at least 5 times) greater than a reference dosage form of the same dosage amount (*e.g.*, a dosage form having 100 mg of VS-6063 relative to a reference dosage form also having 100 mg of VS-6063). In an embodiment, the C_{max} value of an oral dosage form described herein is at least 1.6 times greater, at least 1.7 times greater, at least 1.8 times greater, at least 1.9 times greater, at least 2 times greater, at least 3 times greater, or at least 4 times greater than a reference dosage form of the same dosage amount.

In an embodiment, an oral dosage form described herein has a reduced food effect relative to a reference oral dosage form, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture. In an embodiment, the difference between the T_{max} value of the fed and fasted states for subjects administered an oral dosage form described herein is less that the difference between the T_{max} value of the fed and fasted states for subjects administered a reference oral dosage form of the same dosage amount, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture.

In an embodiment, an oral dosage form described herein has consistent exposure when administered to a subject. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 50% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 40%, 30%, 20%, or 10% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount.

In one aspect, the present ~~invention~~ disclosure comprises an oral dosage form comprising: VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride) in an amount from about 10 to 15% by weight on a dry weight basis, a pharmaceutically acceptable excipient (*e.g.*, a binder (*e.g.*, polyvinyl pyrrolidone (*e.g.*, polyvinyl pyrrolidone vinyl acetate copolymer

(PVP/VA), Copovidone))) in an amount from about 15 to 25% by weight on a dry weight basis, a second pharmaceutically acceptable excipient (*e.g.*, a binder (*e.g.*, polyvinylactate (*e.g.*, Soluplus))) in an amount from about 15 to 25% by weight on a dry weight basis, a pharmaceutically acceptable filler (*e.g.*, polyol (*e.g.*, mannitol-starch (*e.g.*, Pearlitol Flash))) in an amount from about 30 to 40% by weight on a dry weight basis, a pharmaceutically acceptable disintegrant (*e.g.*, crospovidone) in an amount from about 5 to 15% by weight on a dry weight basis, and a pharmaceutically acceptable lubricant (*e.g.*, magnesium stearate) in an amount from about 0.2 to 1.5% by weight on a dry weight basis.

In some embodiments, the VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), is present at 10% weight of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), per weight of the oral dosage form. In some embodiments, the VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), is present at 25% weight of VS-6063, or a pharmaceutically acceptable salt thereof, per weight of the oral dosage form. In some embodiments, the VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), is present at 50% weight of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), per weight of the oral dosage form.

In some embodiments, the physical blend or mixture is provided by a spray dried dispersion process. In some embodiments, the process provides a solid dispersion comprising at least 10% by weight (*e.g.*, 10, 20, 25, 40, 50% or more) of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride). In some embodiments, the process provides a solid dispersion comprising 10% by weight of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride). In some embodiments, the process provides a solid dispersion comprising 25% by weight of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride). In some embodiments, the dispersion further comprises a polymer, *e.g.*, a polymer matrix (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMACS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M; Hydroxypropyl Methylcellulose Phthalate (HPMCP) or Hypromellose Phthalate, *e.g.*, HPMCP-HP55, HPMCP-HP55S, Methocol E3LV, PVP-VA, Soluplus, PVAP, polymethacrylic acid (*e.g.*, Eudragit, *e.g.*, Eudragit L100-55), Soluplus:PVP-VA mixture, Soluplus, HPMCAS (*e.g.*, HPMCAS-H) mixture). In some embodiments, the dispersion further comprises a polymer matrix (*e.g.*, polymethacrylic acid (*e.g.*, Eudragit, *e.g.*, Eudragit L100-55)).

In one ~~aspect~~embodiment, the present ~~invention~~ disclosure comprises an oral dosage form comprising VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), for use

in treating a subject having been identified with a cancer disorder (*e.g.,* mesothelioma (*e.g.,* malignant pleural mesothelioma, *e.g.,* surgical resectable malignant pleural mesothelioma), breast cancer (*e.g.,* triple negative breast cancer), ovarian cancer (*e.g.,* advanced ovarian cancer), lung cancer (*e.g.,* non-small cell lung cancer (NSCLC), *e.g.,* KRAS mutant NSCLC)), or a non-hematolotic malignancy. In one aspect, there is provided the use of an oral dosage form comprising VS-6063 (*e.g.,* VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.,* VS-6063 hydrochloride), in the manufacture of a medicament for treating a subject having been identified with a cancer disorder (*e.g.,* mesothelioma (*e.g.,* surgical resectable malignant pleural mesothelioma), triple negative breast cancer, ovarian cancer (*e.g.,* advanced ovarian cancer), lung cancer (*e.g.,* non-small cell lung cancer (NSCLC), *e.g.,* KRAS mutant NSCLC)), non-hematolotic malignancies).

In one aspect, there is provided the use of an oral dosage form comprising 10 to 500 mg of VS-6063 (*e.g.,* VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.,* VS-6063 hydrochloride), in the manufacture of a medicament for treating a disorder in a patient in need thereof. In one ~~aspect~~embodiment, the present ~~invention~~ disclosure comprises a method of treating a disorder in a patient in need thereof, the method comprising administering an oral dosage form comprising 10 to 500 mg of VS-6063 (*e.g.,* VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.,* VS-6063 hydrochloride), to thereby treat the disorder. In some embodiments, the disorder is a cancer disorder (*e.g.,* mesothelioma (*e.g.,* surgical resectable malignant pleural mesothelioma), breast cancer (*e.g.,* triple negative breast cancer, ovarian cancer (*e.g.,* advanced ovarian cancer)), lung cancer (*e.g.,* non-small cell lung cancer (NSCLC), *e.g.,* KRAS mutant NSCLC)), or a non-hematolotic malignancy.

In some embodiments, the administration is performed in combination with administration of an additional agent (*e.g.,* an anti-cancer or anti-tumor agent, *e.g.,* taxane, *e.g.,* paclitaxel).

In one ~~aspect~~embodiment, the present ~~invention~~ disclosure comprises a method for preparing a direct compressed tablet in unit dosage form, which comprises: (a) admixing (*e.g.,* blending) as a % by weight on a dry weight basis: (i) 5 to 50% by weight on a dry weight basis of VS-6063; (ii) a pharmaceutically acceptable excipient (*e.g.,* a binder, *e.g.,* polymer, *e.g.,* a precipitation inhibitor, *e.g.,* HPMC, *e.g.,* HPMC-AS, *e.g.,* HPMCAS-H, HPMCAS-M, HPMCAS-HF); and (iii) at least one pharmaceutically acceptable excipient selected from a pharmaceutically acceptable filler, a pharmaceutically acceptable disintegrant, and a pharmaceutically acceptable lubricant; to form a VS-6063 formulation in the form of a tabletting powder, capable of being directly compressed into tablets; and (b) compressing the formulation prepared during step (a) to form the compressed VS-6063 tablet in unit dosage form. In one aspect, there is provided a method for preparing a direct compressed tablet in unit dosage form, which comprises: (a) admixing (*e.g.,* blending) as a % by weight on a dry weight basis: (i) 5 to 50% by weight on a dry weight basis of VS-6063; (ii) an excipient (*e.g.,* a binder, *e.g.,* polymer, *e.g.,* a precipitation inhibitor, *e.g., e.g.,* HPMC, *e.g.,* HPMCAS, *e.g.,* HPMCAS-HF); and (iii) at least one excipient selected from a filler, a disintegrant, and a lubricant; to form a VS-6063 formulation in the form of a tabletting powder, capable of being directly compressed into a tablets; and (b)

compressing the formulation prepared during step (a) to form the compressed VS-6063 tablet in unit dosage form. In some embodiments, a pharmaceutically acceptable filler is present at 30 to 60% by weight on a dry weight basis. In some embodiments, a pharmaceutically acceptable distintegrant is present at 2.5 to 5% by weight on a dry weight basis. In some embodiments, a pharmaceutically acceptable lubricant is present at 0.5 to 2% by weight on a dry weight basis.

In one ~~aspect~~embodiment, the present ~~invention~~ disclosure comprises a method of treating a subject having mesothelioma, *e.g.,* malignant pleural mesothelioma, *e.g.,* surgical resectable malignant pleural mesothelioma (*e.g.,* non-metastatic, unresectable), comprising: providing an effective amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); to said subject, thereby treating said subject. In some embodiments, the method comprises providing an effective

embodiments, said therapeutic agent comprises a drug other than a platin drug, *e.g.,* it comprises a taxane, *e.g.,* docetaxel, paclitaxel; a plant derived anti-cancer or anti-tumor substance, *e.g.,* an alkaloid, *e.g.,* vinorelbine; an anti-metabolite, *e.g.,* gemcitabine; or a cytotoxic topoisomerase inhibiting agent, *e.g.,* irinotecan.

In one ~~aspect~~embodiment, the present ~~invention~~ disclosure comprises a method of treating a subject having cancer, *e.g.,* lung cancer, *e.g.,* non-small cell lung cancer (NSCLC), *e.g.,* KRAS mutant NSCLC, comprising: providing an effective amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); to said subject, thereby treating said subject. In some embodiments, the method comprises providing an effective course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); to said subject. In some embodiments, said cancer is metastatic. In some embodiments, the subject has a locally recurrent disease.

In one ~~aspect~~embodiment, the present ~~invention~~ disclosure comprises a method of evaluating a subject having cancer, *e.g.,* lung cancer, *e.g.,* non-small cell lung cancer (NSCLC), for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); comprising: acquiring, *e.g.,* directly or indirectly acquiring, the mutation status of a gene in said NSCLC, thereby evaluating said subject. In some embodiments, the gene is selected from the group comprising KRAS, INK4a/Arf, and p53. In some embodiments, the method comprises acquiring the mutation status of KRAS in said NSCLC. In some embodiments, the method comprises acquiring the mutation status of KRAS and INK4a/Arf in said NSCLC. In some embodiments, the method comprises acquiring the mutation status of KRAS and p53 in said NSCLC. In some embodiments, the method comprises acquiring the mutation status of KRAS, INK4a/Arf, and p53 in said NSCLC. In some embodiments, the method comprises, responsive to said mutation status, selecting said subject for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, responsive to a determination that the NSCLC comprises a KRAS mutant, selecting said subject for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, responsive to a determination that the NSCLC comprises a KRAS mutant and a INK4a/Arf mutant, selecting said subject

across multiple subjects of less than 40%, 30%, 20%, or 10% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount.

In one ~~aspect~~embodiment, the present ~~invention~~ disclosure comprises a unit dosage form having 50 to 800 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 50 +/-25 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 50 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the present ~~invention~~ disclosure comprises a unit dosage form having 100 to 800 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 100 +/-50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 100 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 100 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 200 +/-50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 200 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 200 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 400 +/-50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof).

In some embodiments, the unit dosage form has 400 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 400 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof).

In one ~~aspect~~embodiment, the present ~~invention~~ disclosure provides a method of treating a subject having ovarian cancer, *e.g.,* advanced or metastatic ovarian cancer, comprising: providing an effective amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) to said subject, and optionally, providing an effective amount of a second therapeutic agent, *e.g.,* an anti-cancer or anti-tumor agent, *e.g.,* mitotic inhibitor, *e.g.,* a taxane, *e.g.,* paclitaxel, to said subject; said amounts, alone or in combination, being effective to treat said subject, thereby treating said subject, wherein, said subject receives more than 100 or 250 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) for at least one day, *e.g.,* for an entire cycle or course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); said subject receives VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) for at least 5, 10, or 15 days; said second therapeutic agent is provided, *e.g.,* on a different course regimen, *e.g.,* not always on the same day as said VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, providing a course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) to said subject, and optionally, providing a course of a second therapeutic agent, *e.g.,* an anti-cancer or anti-tumor agent, *e.g.,* mitotic inhibitor, *e.g.,* a taxane, *e.g.,* paclitaxel, to said subject, said courses, alone or in combination, being effective to treat said subject.

In one ~~aspect~~embodiment, the present ~~invention~~ disclosure provides a method of evaluating a subject having ovarian cancer for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable

oral dosage form of the same dosage amount, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.,* Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.,* Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.,* HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture.

In an embodiment, an oral dosage form described herein has consistent exposure when administered to a subject. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 50% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 40%, 30%, 20%, or 10% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount.

In one ~~aspect~~embodiment, the present ~~invention~~ disclosure comprises a unit dosage form having 50 to 800 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 100 +/-50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 100 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 100 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 200 +/-50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 200 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 200 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 400 +/-50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as described herein, *e.g.,* a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 400 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.,* a composition as

49. The oral dosage form of claim 47, wherein the process provides a solid dispersion comprising 10% weight of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride).

50. The oral dosage form of claim 47, wherein the process provides a solid dispersion comprising 25% weight of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride).

51. The oral dosage form of claim 47, wherein the dispersion further comprises a polymer matrix (*e.g.*, HPMACS (*e.g.*, HPMCAS-H, HPMCAS-M), HPMCP (*e.g.*, HPMCP-HP55, HPMCP-HP55S), Methocol E3LV, PVP-VA, Soluplus, PVAP, Eudragit L100-55, Soluplus:PVP-VA mixture, Soluplus, HPMCAS (*e.g.*, HPMCAS-H)) mixture.

52. The oral dosage form of claim 51, wherein the dispersion further comprises a polymer, *e.g.*, polymer matrix (*e.g.*, polymethacrylic acid (*e.g.*, Eudragit L100-55)).

53. Use of a~~A~~n oral dosage form comprising VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), ~~for use~~ in the manufacture of a medicament for treating a subject having been identified with a cancer disorder (*e.g.*, mesothelioma (*e.g.*, surgical resectable malignant pleural mesothelioma), triple negative breast cancer, ovarian cancer (*e.g.*, advanced ovarian cancer), lung cancer (*e.g.*, non-small cell lung cancer (NSCLC), *e.g.*, KRAS mutant NSCLC)), non-hematolotic malignancies).

54. ~~A method of treating a disorder in a patient in need thereof, the method comprising administering~~ Use of an oral dosage form comprising 10 to 500 mg of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), in the manufacture of a medicament for treating a disorder in a patient in need thereof~~to thereby treat the disorder~~.

55. The ~~method~~ use of claim 54, wherein the disorder is a cancer disorder (*e.g.*, mesothelioma (*e.g.*, surgical resectable malignant pleural mesothelioma), breast cancer, *e.g.*, triple negative breast cancer, ovarian cancer (*e.g.*, advanced ovarian cancer), lung cancer (*e.g.*, non-small cell lung cancer (NSCLC), *e.g.*, KRAS mutant NSCLC)), non-hematolotic malignancies).

56. The ~~method~~ use of claim 54, wherein the administration is to be performed in combination with administration of an additional agent (*e.g.*, cancer therapeutic, *e.g.*, taxane, *e.g.*, paclitaxel).